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GUEST EDITORIAL

Children Will Benefit as Pediatric Groups Merge: A Surgical Oncologist's Perspective

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INTRODUCTION

As the new millennium unfolds, the most important global development in pediatric surgical oncology relates to the dramatic impact from the decision of the four pediatric cancer clinical trials cooperative groups in North America to form a single entity. This complex decision emanated from a 4-year pediatric intergroup summit process and parallels the effort of the National Cancer Institute (NCI) to revise the clinical trials system. These events may have profound effects on the newly formed American College of Surgeons Oncology Group (ACOS-OG), the surgical oncology community at large, and pediatric surgical oncology in particular. Therefore, it seems appropriate to chronicle the issues and provide the journal readership an insight into the background, structure, and proposed time table for the pediatric group merger.

In general, the impact of children's cancer continues to be understated in the overall oncology world. Other than congenital disease, cancer remains the most common cause of death from illness among children, adolescents, and young adults in the United States [1]. The cancer incidence rate in children younger than 15 years of age is increasing by 1% per year, whereas the cure rate is increasing by 1.4% per year [2]. Thus, pediatric cancer ranks below only breast and lung cancer in the total number of person-years of potential life at risk at approximately 550,000 patient-years. In addition, it is second only to breast cancer in the number of person-years of potential life saved at nearly 400,000 person-years [3]. Young patients show a survival rate approaching 80% with current multimodality therapy. Therefore, it can be anticipated that by the year 2000, there will be more than 200,000 survivors of childhood cancer in this country.

A geographic analysis of the distribution of pediatric cancer in the United States, including observed/expected ratios of disease in different regions, has been undertaken. This study evaluated census data and incidence rates from the surveillance, epidemiology, and end results (SEER) program of the NCI [4]. The institutional networks of the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) involve essentially the entire country and treat cancer in 98% of children ages birth to 4 years, 93% of those ages 5–9 years, 84% of those ages 10–14 years, and 21% of those ages 15–19 years. Because less than 3% of patients under 20 years of age were entered on NCI-sponsored protocols conducted by the adult cooperative groups, the majority of patients ages 15–19 with cancer may not be receiving the most effective therapies. This is of concern because adolescents and young adults with malignancy demonstrate better survival rates when they are managed on multidisciplinary treatment protocols sponsored by the pediatric cooperative groups when compared with patients not registered on clinical trials [5,6].

In this light, pediatric cancer trials require "centers of excellence" because they are intensive, multidisciplinary, and generate a complex societal impact. Issues of long-term survivorship, epidemiology, psychosocial and supportive care, and the late effects of treatment including quality of life assessment are vital yet problematic to assess [7]. The concept of superior surgical outcomes from experienced teams and centers has already been demonstrated in adult surgical oncology [8–13]. A similar impact for cancer surgery in children can only be effectively analyzed as part of a unified multimodality system of therapy programs. It is this new direction for a merged national pediatric effort that I want to describe and emphasize in the following commentary.

It is not surprising that the 1997 report of the Clinical Trials Program Review Group chaired by James Armit-

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age partially described the current system as increasingly complex, inefficient, and with a resultant decreased ability to generate new ideas and reduce the cancer burden. A Clinical Trials Implementation Committee chaired by John Glick and Michaele Christian, Director of the NCI Cancer Therapy Evaluation Program (CTEP), was subsequently charged with responding to the review and developing plans for extensive system-wide improvements including enhancing scientific strategies, overcoming barriers to patient accrual, and improving program funding. This latter issue has been the source of significant dissatisfaction for many years. As an example, a particular adult cooperative group's statistical center recently achieved an outstanding priority score through peer review, but received only a 3% increase above funding base. Although there have been subsequent financial supplements, the underlying problem remains.

The NCI generally awards the cooperative groups only about 50% of the amount recommended by the Cancer Clinical Investigations Research Committee. The implications for only "trickle down" support for surgical efforts from a predominantly oncology-oriented program are indeed ominous and the formation of the ACOS-OG may be critical to surgeons in this regard. In response to these concerns, the NCI has committed to double cooperative group funding over the next several years to provide consistent reimbursement for scientific leadership and patient accrual.

The Implementation Committee report was presented to the NCI Board of Scientific Advisors in September 1998 and was promptly accepted. It suggested that changes be instituted to address multidisciplinary scientific questions especially in the areas of epidemiology, prevention, treatment, quality of life, outcomes research, and long-term follow-up. A new system for effective research prioritization would involve initiatives in limited institution pilots, small developmental studies, translational research, and definitive clinical trials. The focus was to emphasize the best science, increase operational efficiency, improve patient accrual, and enhance funding. The concept of cross group registrations by disease type could augment a network of multidisciplinary, multiinstitutional centers of excellence, a model that has worked exceptionally well in surgical and pediatric oncology [6,9,13,14].

In this new environment for clinical investigation, the overriding principles of NCI-sponsored cancer cooperative groups would be maintained. There remains a commitment to maximize the number of patients with an opportunity to participate in high-quality trials, decrease the barriers to physician involvement and patient accrual, complete studies in a timely manner, and translate new basic and clinical findings into current practice. This new spectrum of activity would retain essential functional elements such as interaction with academic centers, community institutions, allied health professionals, and biostatistics and data management expertise.

It is within this context of shifting sands in the adult oncology world that the pediatric cancer care and research issues can be assessed. Cognizant of the increasing problems with the clinical trials system, the leadership of CCG and POG held their first joint meeting in May 1995. This landmark conference began a strategic planning process for protocols of interaction with the initial intent to improve communication and intergroup studies. This led to a broad bilateral commitment to collaborate and started the concept of "Intergroup Day," an opportunity for cross invitations of rotating discipline members from each organization to attend the semiannual meeting of the other. This process was initiated when CCG surgeons and statisticians for the first time attended the POG meeting in October 1995.

Ironically, during 1995, the NCI was undergoing a period of change in leadership and structure. CTEP investigators communicated to the chairs of the pediatric cooperative groups that there was a perception that the treatment of childhood malignancies had been so successful that further research in the field was no longer required. Fortunately, the NCI hierarchy did not agree with this because many children were still dying of cancer and the long-term morbidity and societal impact were high. However, there was concern that the pediatric groups were perceived as being adverse to collaborating with each other and, therefore, not conducting their clinical research as efficiently as possible. Also, regardless of the communication that did occur, the groups had the propensity to develop their scientific agendas in relative isolation and to become too deeply invested in their own lines of investigation such that intergroup studies could not be effectively accomplished.

In response to this potential criticism, the pediatric investigators reported that more than 1 in every 6 clinical trial entries by CTEP-sponsored cooperative groups were in childhood patients. In addition, more than 94% of children with cancer in the United States under the age of 15 were registered by either CCG or POG and more than one half were entered in one or more clinical trials [15]. It was recognized that pediatric cancer care was more complex, more multiphasic, and of longer duration than the treatment of most adult patients. Chemotherapy was also more intensive in terms of number, combination, and permutation of drugs used and, therefore, had a greater potential for delayed and late adverse effects. A lifetime of follow-up is needed and the eventual impact on growth, development, education, employment, and societal function has yet to be analyzed.

Nevertheless, this "challenge" from CTEP markedly accelerated the collaborative activities among the pediatric scientists. Another Intergroup Day took place at the

CCG meeting in November 1995 followed by a joint CCG-POG meeting of radiation oncologists at the 1996 annual symposium of the American Society of Therapeutic Radiology and Oncology. A second summit was held in July 1996 in Chicago where intergroup study process issues were identified in a more detailed manner, policies were established, and operations were streamlined. Single joint study committees were formed, opportunities for intergroup patient transfers were made, and the regular exchange of study data was initiated. Subsequent Intergroup Days also occurred at the POG and CCG meetings in October and November 1996, respectively.

These interactions continued to mature throughout 1997. During this time, both major pediatric cooperative groups initiated scientific and structural reorganizations. The CCG programs could be depicted by a matrix alignment, each managed by a group vice-chair with scientific affairs and translational research on one side and multidisciplinary and intergroup programs on the other. In the former division, 3 associate chairs manage disease and epidemiology strategy groups with reference and resource laboratories representing studies in leukemia, solid tumors, new agents, pharmacology, and biotherapy. In the latter division, a steering committee directs discipline committees such as surgery, radiotherapy, and pathology, scientific committees such as supportive care and local tumor control, and administrative committees such as publications, membership, data monitoring, and informatics.

Although it was desirable to maintain the research continuity of these longstanding successful systems, the CCG leadership recognized that a new biology and translational research program must be designed and implemented. This program encompassed basic science and translational research in the areas of molecular diagnostics, cytogenetics, epidemiology, and cancer control as well as experimental therapeutics, molecular and gene therapies, and prevention strategies. This structure also interacted intimately with the biopathology center and the Cooperative Human Tissue Network. Similar programs were being formulated by the POG and to some degree by the other two pediatric cooperative groups, the Intergroup Rhabdomyosarcoma Study Group (IRSG) and the National Wilms Tumor Study Group (NWTSG). However, it was clear that the 4 groups were expending enormous energy and duplicating much activity. The redundancies in scientific, technical, and regulatory areas were also becoming increasingly obvious and further work would need to be done.

With these goals in mind, a third summit meeting was held in Chicago on July 17–18, 1998 for the purpose of condensing the pediatric intergroup process. As the discussion evolved regarding a national agenda for childhood cancer, it became evident that the best solution lay in the formation of a single pediatric cancer clinical trials organization. At the fall 1998 POG and CCG meetings, the leadership overwhelmingly endorsed the motion to create a single entity and this was subsequently approved by the executive committees of the IRSG and NWTSG. Because the member institutions of the pediatric groups provide virtual complete geographic coverage of North America, it would now be possible to produce a childhood oncology registry and perform population-based studies of pediatric cancer epidemiology and cancer control which could expand on currently available data bases [16]. The opportunities to broaden research horizons and increase involvement of investigators would allow the design and conduct of studies previously impossible to accomplish. With enhanced capacity, the consolidated organization might improve the number of children with cancer on therapeutic trials from the current 55% to the 80–90% range. If the ultimate outcome was successful in increasing accrual, completing studies more rapidly, enhancing biologic studies, and avoiding the complexities of intergroup trials, the care of children and young adults with cancer could be predicted to dramatically improve.

It must be realized that this complex decision was a firm commitment to create an entirely new entity not merely to merge or integrate the previous groups. Properly accomplished, this could create efficiencies in study design and development of prevention, diagnosis, and treatment strategies, as well as improve multidisciplinary scientific output in surgery, radiation therapy, and biopathology. The effort would also enhance technical areas such as statistics, data management, and computer informatics and decrease regulatory redundancies in credentialing, audits, institutional review, and drug distribution controls. The new organization could now focus on clinical care and scientific research and allocate proportionally less effort to operations, technical issues, and regulation. Such a unified group would be able to forge more cohesive strategic partnerships with the pharmaceutical industry, managed care and other payors, independent research groups, advocacy organizations, foundations and institutes, and the public at large. This overall effort also parallels the clear direction of the NCI to enhance funding levels for each cooperative group with the proviso that appropriate coalitions may eventually result in a lower total number of these clinical trials entities.

Once the agreement to form this new multidisciplinary pediatric group was endorsed, the real work began. Malcolm Smith of CTEP expressed the NCI's support of this decision and described the fusion as a major "paradigm shift." The NCI recognized that supplemental funding would be necessary to accelerate the work of the integration efforts. The first "new group" retreat was held in Virginia on March 19–20, 1999. Richard Ungerleider, Chief of the Clinical Investigations Branch, representing NCI Director Richard Klausner, said the Institute was "fully supportive of the merger and was very pleased

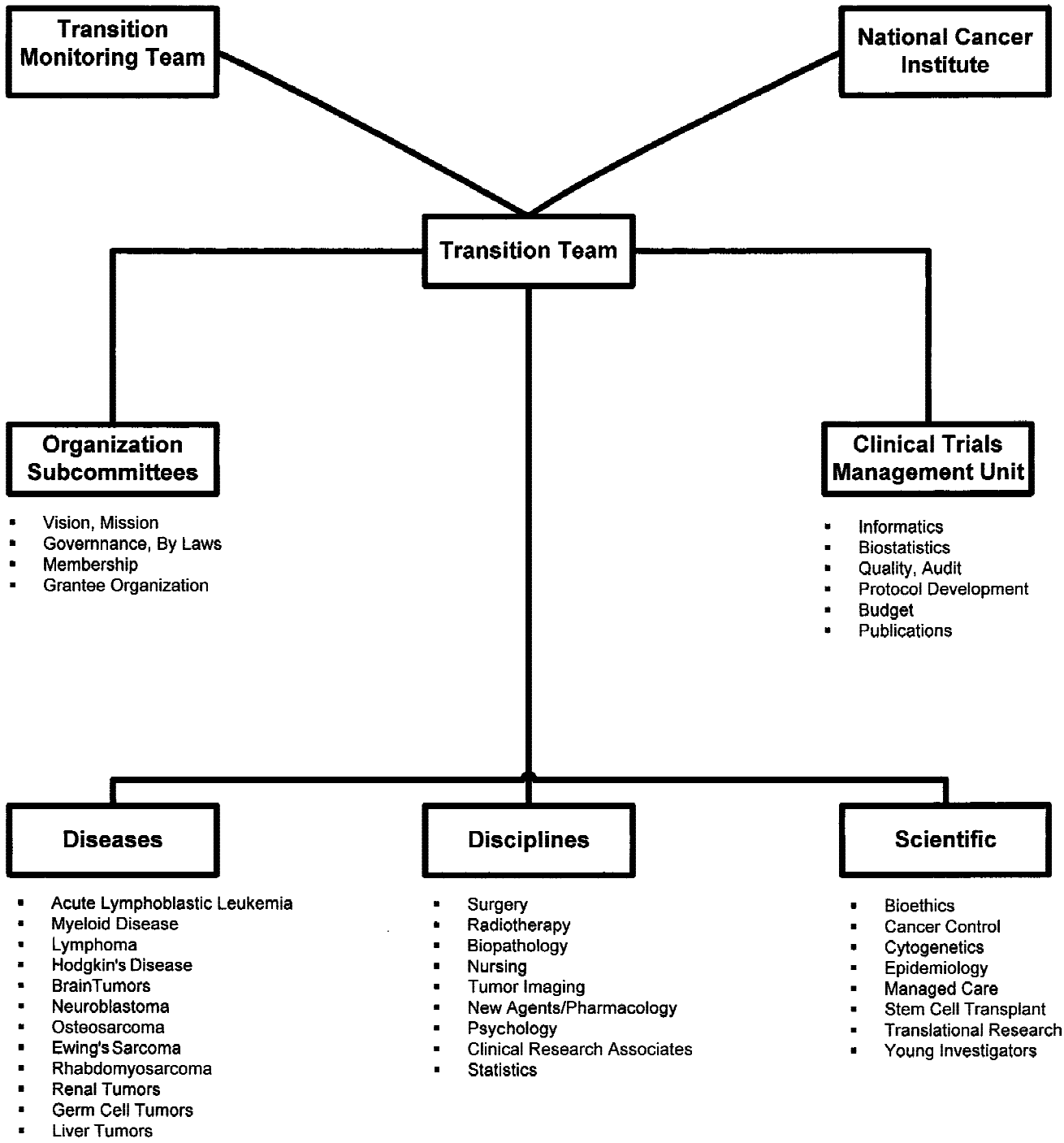

Fig. 1. Leadership structure for integration of new pediatric group.

with the announcement." The fusion should ensure the survival of the pediatric cancer mission into the next millennium to optimize the cure rate and long-term quality of life.

A system of working committees and task forces were rapidly developed to consider issues of membership, organizational structure, constitution, and by-laws and funding mechanisms. The cross attendance at respective group meetings continues to the present time and is planned with the disease-based working committees on leukemia and solid tumors alternating attendance at meetings throughout the process. Minimum essential institutional requirements for membership in the new group will be established and, in part, will parallel the guidelines for pediatric cancer centers as published by the American Academy of Pediatrics [17]. The effort

would also enhance the partnership with managed care such as the program developed by the Blue Cross/Blue Shield association with its "Blues Quality Centers for Pediatric Cancer." This payor arrangement identifies a network of member institutions that provide appropriate personnel, facilities, and quality of care for those insured children diagnosed with cancer.

The interim organizational structure for this project centers around a leadership transition team ultimately charged with final decision-making (Fig. 1). The membership is made up of the group chairs, vice-chairs, statisticians, executive officers, discipline committee chairs, and informatics managers. There is also an external transition monitoring team representing different constituencies which reviews plans and communications of the transition team and provides input into overall process and function. Joint task forces have been formulated, each composed of appropriate individuals representing the disease committees, disciplines, scientific support committees, and administrative infrastructure. There are 12 disease strategy groups, 9 discipline committees, and 8 scientific support committees. There are also specialized subcommittees analyzing issues such as vision and mission, governance, constitution and by-laws, grantee organization and foundation relationships, institutional and individual membership and clinical trials management.

The new organization has recently been named and will be known as the Children's Oncology Group (COG). Ratification of its constitution and by-laws by the voting bodies of POG, CCG, NWTSG, and IRSG is planned for early in the year 2000. The first formal COG meeting will be held in March 2000. A nominating committee will begin the process of screening group chair candidates. Importantly, the discipline committee chairs will be elected by their constituencies so that the pediatric surgeons will select the surgery committee chair who will be a permanent member of the COG governing board. This should preserve the opportunity for surgical centers of excellence to remain directly involved in pediatric cancer care and research trials. Also, the relationship between appropriate COG surgery leadership and the ACOS-OG can be fostered for obvious bilateral benefit. Finally, the new group chair will take office in January 2001 and the governing board will be assembled in March 2001 to launch the full spectrum of COG activities.

There are certainly risks in any new venture and this one is not immune. There is obviously concern regarding decreased competitiveness and the rigor of peer review because there will now only be a single pediatric cooperative clinical trials organization. The NCI is vitally interested in the appropriate integration of guidelines that will establish scientific leadership, maintain intellectual competition, develop streamlined processes for concept review and pilot studies, and effectively incorporate translational research into clinical trials. It may be necessary to develop a scientific advisory board drawn from adult oncology and international bodies of pediatric oncology to review and critique the COG science and directions.

Ultimately, COG will have the potential for more and accelerated phase 1 studies and will be challenged to get new trials ready for entry much more rapidly because the previous ones will be completed sooner. Parallel study development committees may be necessary to ensure appropriate timelines and prevent prolonged periods with no open studies. It will be critical that mechanisms for evaluating competing ideas are built into the infrastructure. The goal should be that virtually all children and young adults can be treated on high-quality clinical trials. The COG should be able to take advantage of better science, faster studies, increased efficiency, and greater funding from federal and private sources. This will further enhance the spectacular cure rates in pediatric oncology and better manage the issues of long-term survivorship, quality of life, and societal impact. Surgical oncologists who care for children, adolescents, and young adults have been intimately involved in the creation of this new multidisciplinary effort and should thrive comfortably within the new unified pediatric cancer cooperative group.

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